

The 2009 pandemic influenza A (H1N1) infection: Renal histopathology findings in two infected patients

Vasco Fernandes¹, Ana Carina Ferreira¹, Helena Viana^{1,2}, Fernanda Carvalho^{1,2}, Ana Vila Lobos¹, Fernando Nolasco¹

¹ Nephrology Department and ² Department of Renal Pathology.
Hospital Curry Cabral. Lisbon, Portugal.

Received for publication: 23/02/2011
Accepted in revised form: 04/11/2011

ABSTRACT

Background: Acute kidney injury in the pandemic swine origin influenza A virus (H1N1) infection has been reported as coursing with severe illness, although renal pathogenic mechanisms and histologic features are still being characterised.

Case Report: We present two patients admitted with H1N1 pneumonia, sepsis, acute respiratory distress syndrome and need for invasive mechanical ventilation who developed acute kidney injury and became dialysis-dependent. In both cases a kidney biopsy was performed to establish a definitive diagnosis. Severe acute tubular necrosis was identified, with no further abnormalities.

Conclusion: This report seems to confirm that the acute kidney injury in H1N1 infection is focused on the tubular cells. Our cases corroborate the renal histopathologic findings of other studies, highlighting the central role of the tubular cell. We bring new evidence of the histopathology of AKI in H1N1 infection since our data were collected in living patients and not via post-mortem studies.

Key-Words:

Acute kidney injury; acute tubular necrosis; H1N1 infection; sepsis.

INTRODUCTION

The year 2009 saw the emergence of a novel influenza A (H1N1) virus of swine origin.

The pandemic strain represented a quadruple reassortment of two swine strains, one human strain and one avian strain of influenza. The largest proportion of genes came from swine influenza viruses, followed by North American avian influenza strains and human influenza strains. Analysis of the antigenic and genetic characteristics of the pandemic H1N1 influenza A virus demonstrated that its gene segments had been circulating for many years, but lack of surveillance in swine is the probable reason this strain went unrecognised prior to the 2009 pandemic¹.

The signs and symptoms of influenza caused by pandemic H1N1 were similar to those of seasonal influenza, although gastrointestinal manifestations appeared to be more common². Disease severity ranged from mild influenza-like illness to multiorgan failure with severe hypoxaemia. Although severe illness was mostly associated with acute lung injury (ALI), postmortem studies evidence renal involvement in H1N1 infection^{3,4}.

Establishing a relationship between a virus and a renal disorder is often problematic, and a simple

documentation of the virus or of the virus particles in the kidney is not enough. It is known that acute kidney injury (AKI) in the setting of viral infections has several histomorphologic features, ranging from glomerular/tubulointerstitial nephritis to acute tubular necrosis (ATN), vasculitis or other renal manifestations⁵.

Viruses can have a direct cytopathic effect on epithelial/tubular cells, as is the case of collapsing glomerulonephritis with human immunodeficiency virus (HIV). Kidney injury can also result from deposition or *in situ* formation of immune complexes containing viral antigens that are most specifically associated with glomerular injury, as in the case of HIV immune complex glomerulonephritis, hepatitis B associated membranous nephropathy or hepatitis C associated membranoproliferative glomerulonephritis with or without cryoglobulinaemia. Less commonly, viruses can lead to fulminant organ failure and AKI, as is the case of Dengue and Hantavirus infection, with different histopathologic features ranging from ATN to acute interstitial nephritis. Moreover, kidney disease can also occur indirectly as the result of the systemic consequences of the infection, such as multiorgan failure, rhabdomyolysis, hepatorenal syndrome, or as a result of its treatment⁵. Nevertheless, histological features of AKI in the setting of H1N1 infection, something that could provide some data on its pathophysiology, are still scarce.

The most common renal histological finding in postmortem patients infected by H1N1 virus was ATN^{3,4}. Although there was no evidence of direct virus-induced kidney injury, Carmona and colleagues found H1N1 viruses in the cytoplasm of glomerular macrophages³ and Nin and co-workers described viral nucleoprotein in tubular cells, such as intracytoplasmatic granules in parietal and visceral glomerular epithelial cells⁴.

The authors report two cases of severe H1N1 infection, diagnosed through viral RNA detection with reverse transcriptase polymerase chain reaction, which became oliguric requiring renal replacement therapy in the first days after hospital admittance. Both survived, and both had a kidney biopsy to establish a definitive diagnosis.

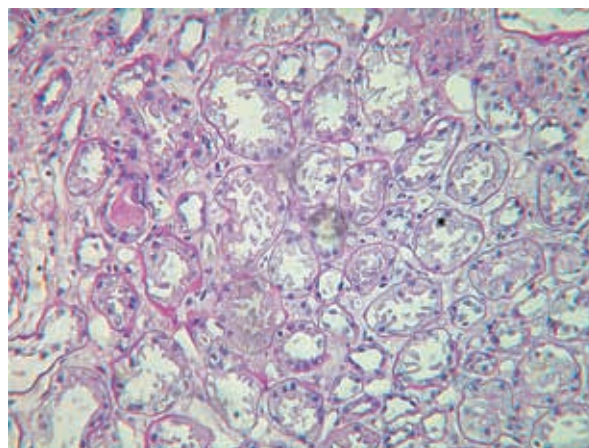


Figure 1

Vacuolisation and necrosis of epithelial tubular cells. Loss of brush border in the epithelial cells (PAS x250).

CASE REPORT 1

A 39-year-old Caucasian female with metabolic syndrome (diabetes, hypertension, dyslipidaemia and obesity) was admitted in ICU with H1N1 viral pneumonia, complicated with acute respiratory distress syndrome (ARDS), respiratory failure and dependence on invasive mechanical ventilation. Although there was no evidence of bacterial infection, vancomycin, ceftriaxone, clarithromycin and oseltamivir were started, and, two days later, circulatory and renal failure developed, requiring noradrenalin and slow low efficiency dialysis (SLED). Serum creatinine (Scr) rose from 0.8 mg/dL to 7 mg/dL, without severe rhabdomyolysis (maximum CK 1400 U/L). After one week she recovered haemodynamic stability, and on the 20th day of admittance she was no longer on mechanic ventilation, but remained dialysis-dependent.

She was transferred to the nephrology ward. At the 6th week a renal biopsy was performed, and no other features besides severe ATN were noted (Fig. 1). At the beginning of the 7th week renal failure improved and she no longer needed dialysis. Two weeks later she was discharged with Scr 1.4 mg/dL, after which she was lost for follow-up.

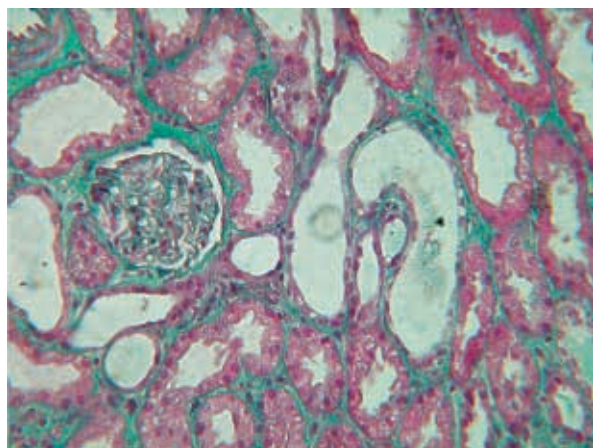


Figure 2

Total loss of epithelial tubular cells in proximal and distal tubules (Trichrome Masson x400).

CASE REPORT 2

A 30-year-old Caucasian male with trigeminal neuralgia was admitted with H1N1 viral pneumonia, complicated with ARDS and sepsis. Although there was no evidence of bacterial infection, vancomycin, meropenem, clarithromycin and oseltamivir were started. One day after admittance invasive mechanical ventilation was begun for refractory respiratory failure. Scr rose from 0.8 mg/dL to 8 mg/dL in three days, in spite of haemodynamic stability along with no significant rhabdomyolysis (maximum CK 460 U/L), and SLED was begun. On the 15th day his pulmonary condition improved and he no longer needed mechanical ventilation, but remained haemodialysis-dependent and was transferred to the nephrology ward.

At the 4th week a renal biopsy was performed and severe ATN was diagnosed (Fig. 2), again without further features. At the beginning of the 5th week renal failure recovered and there was no need for dialysis. He was discharged 12 days later with Scr 2.9 mg/dL. Almost three months after the beginning of H1N1 infection renal function normalised with Scr 1.0 mg/dL and normal dipstick urine analysis.

DISCUSSION

H1N1 infection has dramatically changed the benign view of viral disease in intensive care units, being associated with sepsis, significant rates of AKI and mortality⁶⁻⁸.

Sepsis or systemic inflammatory response syndrome is a serious condition, characterised by a whole-body inflammatory state in consequence of an infection⁹, mostly due to bacteria, less frequently a fungus, and rarely related to a virus⁸. This severe condition leads to multiple organ failure, and the kidney is frequently affected and associated with high mortality⁹.

Pathophysiology of AKI in sepsis is complex and seems to be related to multiple factors. The most important appears to be associated with haemodynamic changes, the so-called hyperaemic injury, that in the kidney is mediated by vasodilatation of afferent and efferent arterioles, accompanied by an increase in renal blood flux, but with decreased glomerular capillary pressure and subsequent decrease in filtration with initial normal tubular function. Other implicated factors are endothelial dysfunction, infiltration of inflammatory cells in renal parenchyma, intraglomerular thrombosis and obstruction of tubules with necrotic cells and debris⁹.

As in sepsis, ARDS is an inflammatory condition, characterised by primary injury to pulmonary endothelium and epithelium, and its proinflammatory effect, in combination with mechanical ventilation, may be a source for AKI¹⁰. Imai and co-workers, using a rabbit model of ALI, have demonstrated that lung injurious ventilator strategies induce apoptosis of proximal tubular cells¹¹, providing evidence of distant organ cross-talk initiated by ALI. Ranieri *et al.* showed, in a randomised controlled trial of 44 patients with ARDS, that a protective mechanical ventilation strategy induced less systemic inflammatory response and led to less organ failure, in particular, fewer patients developed AKI¹².

Sepsis, AKI, need for renal replacement therapy, and mortality related to H1N1 infection have led to an effort to better characterise and understand the mechanisms of kidney injury in this kind of viral

infection. As already highlighted by Joannidis and Forni, hypovolemia and vasodilatory shock due to host exaggerated response appear to be the main aetiological factors⁸. Rhabdomyolysis has also been mentioned as playing a role in the pathogenesis of tubular injury, but historical data mention that creatine kinase levels normally associated with kidney injury are above 5000 U/L, making it less likely as the main aetiological factor in the tubular injury¹³. Other possible factors are bacterial co-infections and associated co-morbidities⁸.

In our report, two patients admitted with sepsis and ARDS were submitted to kidney biopsy after 6 and 4 weeks of dialysis dependence. ATN was the histological pattern of AKI in the setting of their H1N1 infection. No evidence of glomerular, tubulointerstitial or endothelial inflammation, and no features of direct cytopathic changes were found. Likewise, there was no evidence of significant rhabdomyolysis, drug toxicity or ongoing bacterial or fungal infection. It would have been interesting to try and identify viral antigens in renal tissue, but since there was no trace of tissue response to viral infection, even if those antigens had been identified, they probably would not have been directly pathogenic. All these data seem to confirm that the kidney injury in H1N1 infection is focused to the tubular cells and could be a consequence of severe systemic inflammatory response syndrome induced by the viral infection. Although there was no description of direct virus-mediated cytopathic damage or immunologic phenomena, our histological findings differ from those reported in patients dying from septic shock (tubular epithelial apoptosis; leucocytic infiltration in glomeruli and capillaries), and therefore the role of direct viral infiltration in the pathogenesis of AKI induced by H1N1 still remains to be established⁸.

Our report corroborates the renal histopathologic findings of other studies^{3,4}, highlighting the central role of the tubular cell. We bring new evidence to the histopathology of AKI in H1N1 infection since our data were collected in living patients and not post-mortem. For now, measures similar to sepsis early-goal directed therapy seem to be the best treatment

to offer⁸, but further research needs to be carried out in the pathogenesis of sepsis-related organ injury and mechanisms of cellular protection, especially on the renal tubular epithelia.

Conflict of interest statement. None declared.

References

- Garten RJ, Davis CT, Russell CA, *et al.* Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 2009;325:197
- Bautista E, Chotpitayasunondh T, Gao Z, *et al.* Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010;362:1708-1719
- Carmona F, Carlotti AP, Ramalho LN, Costa RS, Ramalho FS. Evidence of renal infection in fatal cases of 2009 pandemic Influenza A (H1N1). *Am J Clin Pathol* 2011;136:416-423
- Nin N, Lorenta JA, Sanchez-Rodriguez C *et al.* Kidney histopathological findings in fatal pandemic 2009 influenza A (H1N1). *Intensive Care Med* 2011;37:880-881
- Berns JS, Bloom RD. Viral nephropathies: core curriculum 2008. *Am J Kidney Dis* 2008;52:370-381
- Abdulkader RC, Ho YL, de Sousa Santos S, Caires R, Arantes MF, Andrade L. Characteristics of acute kidney injury in patients infected with the influenza A (H1N1) virus. *Clin J Am Soc Nephrol* 2010;5:1916-1921
- Pettila V, Webb SA, Bailey M, Howe B, Seppelt IM, Bellomo R. Acute kidney injury in patients with influenza A (H1N1) 2009. *Intensive Care Med* 2011;37:763-767
- Joannidis M, Forni L. Severe viral infection and the kidney: lessons learned from the H1N1 pandemic. *Intensive Care Med* 2011;37:729-731
- Zarjou A, Agarwal A. Sepsis and acute kidney injury. *J Am Soc Nephrol* 2011;22:999-1006
- Koyner JL, Murray PT. Mechanical ventilation and lung-kidney interactions. *Clin J Am Soc Nephrol* 2008;3:562-570
- Imai Y, Parodo J, Kajikawa O, *et al.* Injurious mechanical ventilation and end organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003;289:2104-2112
- Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000;284:43-44
- Huerta-Alardín A, Varon J, Marik P. Bench-to-bedside review: Rhabdomyolysis – an overview for clinicians. *Critical Care* 2005;9:158-169

Correspondence to:

Dr Vasco Fernandes
Department of Nephrology
Hospital Curry Cabral
Rua da Beneficência
1069-166 Lisbon, Portugal
email: vasco.rbf@gmail.com